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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/874,040 | 06/06/2001 | James Robl | P 280633 23523-0008 | 8078 |

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| EXAMINER |
|---|
| WEHBE, ANNE MARIE SABRINA |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SRM

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/874,040 | ROBL ET AL. | |
| | Examiner | Art Unit | |
| | Anne Marie S. Wehbe | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *36-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/8/03 has been entered. As requested, the amendment filed on 3/10/03 and accompanying declaration under 37 CFR 1.132 have been entered. Claims 36-87 are currently pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

### *Claim Rejections - 35 USC § 103*

The rejection of claims 36-87 under 35 U.S.C. 103(a) over Wolfe et al. in view of Collas et al. is withdrawn in view of applicant's amendment to the claims to recite wherein the NT unit is capable of giving rise to a multicellular structure of at least about 50 cells, and further in view of the declaration by Robert Lanza under 37 CFR 1.132.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 36-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 51-66, 69-102 and 105-146 of copending Application No. 09/685,061, hereafter referred to as the '061 application. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. Claims 51-66, 69-102 and 105-146 of '061 application represent a species of the instant claims in that the '061 claims are limited to nuclear transfer between ungulates while the instant claims broadly read on nuclear transfer between any two different animal species. It is well established that a species of a claimed invention renders the genus obvious. *In re Schaumann* , 572 F.2d 312, 197 USPQ 5 (CCPA 1978). Therefore, as a species of the instant claims, claims 51-66, 69-102 and 105-146 of the '061 application render obvious instant claims 36-87.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 36-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-52 of copending Application No. 09/809,018, hereafter referred to as the '018 application. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. Claims 36-52 of '018 application represent a species of the instant claims in that the '018 claims are limited to nuclear transfer between a human cell and a bovine oocyte while the instant claims broadly read on nuclear transfer between any two different animal species. It is well established that a species of a claimed invention renders the genus obvious. *In re Schaumann* , 572 F.2d 312, 197 USPQ 5 (CCPA 1978). Therefore, as a species of the instant claims, claims 36-52 of the '018 application render obvious instant claims 36-87.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-87 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The applicant claims methods for producing a nuclear transfer (NT) unit having genomic DNA or one mammalian species and mitochondria of a different mammalian species and being capable of giving rise to a multicellular structure of at least 50 cells, and isolated embryonic cells and cell lines derived from said multicellular structure. Please note that the claims broadly read on the transfer of genomic DNA from a differentiated donor cell from any mammalian species to an oocyte from any mammalian species different from the donor mammalian species. Although certain dependent claims limit the donor cell origin to ungulate species or to a human, see claims 46-48, 54, 63-64, 66-67, 70-71, 77-78, and 83-48, or the oocyte species to ungulates or primates, 50-53, 64, 67, 71, 77-78, and 84, the independent claims and remaining dependent claims are not so limited. In addition, the claims read broadly on numerous types of differentiated donor cells, including differentiated germ cells, somatic cells, and differentiated embryonic cells. Only claims 40-45, and 47 place any limitation on the characteristics of the differentiated donor cell.

The specification is directed to the production of pluripotent embryonic cells, specifically embryonic stem cells, through the use of cross-species nuclear transfer. Pages 6-7 of the specification clearly teach that the purpose of producing embryonic cells using the disclosed methods is for the production of a stem

cell population useful in therapeutic transplantation and gene therapy of diseases including

Parkinson's disease. The specification also teaches that the methods of cross-species NT can be used to produce live animals or transgenic animals.

At the time of filing, cross-species nuclear transfer was considered highly unpredictable. The declaration under 37 CFR 1.132 by Dr. Robert Lanza provides a detailed analysis of the state of the art of cross-species nuclear transfer and identifies numerous factors which contribute to the complexity and unpredictability of the field. The factors include: 1) differentiated cells may have lost the capacity to direct embryonic development , i.e. differentiated cells may not be able to reactivate essential developmental genes due to inactive chromatin or transcriptionally inactive genes ; 2) evolutionary divergence of the structures of the nuclear chromatin relative to the corresponding oocyte components could result in structural incompatibilities that inhibit or alter reactions required for successful embryogenesis; 3) the complement of proteins initially produced by an embryonic genome varies from species to species; 4) the stage of the switch from maternal to embryonic gene transcription varies from species to species; and 5) incompatibilities between oocyte-derived mitochondria and proteins expressed by the donor nuclear genes. In regards to 5), Dr. Lanza reports that Kenyon et al. have demonstrated impaired oxidative phosphorylation in cells with human genomic DNA and orangutan, new world monkey, or lemurs mitochondrial DNA (Kenyon et al. (1997) PNAS, Vol. 94, 9131-9135). Further, in comparing cross-species nuclear transfer with intra-species nuclear transfer, Dr. Lanza states on page 3 of the declaration that, ".. it was recognized that reprogramming following inter-specific nuclear transfer was even more complex and unpredictable than reprogramming associated with intra-specific nuclear transfer, because all of the complex reactions and interactions between the nuclear chromatin and components of a recipient oocyte that are required for embryonic

development would have to occur across the evolutionary divide between the two species." Finally, having reviewed all of the potential problems associated with cross-species nuclear transfer, Dr. Lanza concludes, " in view of the combined effects of structural incompatibilities between the proteins of the nuclear chromatin and oocyte components that could interfere with reprogramming, together with species-dependent asynchronies in the timing and pattern of embryonic gene expression, and discordance between genome- and oocyte-derived mitochondrial proteins, persons of ordinary skill in the art at the time the parent application was filed could not have predicted whether or not interspecies nuclear transfer using differentiated donor cell nuclei would lead to successful embryonic development and production of blastocysts" (Lanza Declaration, page 7). Thus, it is clear that at the time of filing, the skilled artisan did not consider cross-species nuclear transfer as well-developed or predictable.

The specification fails to provide sufficient description of the instant invention to overcome the high degree of unpredictability associated with cross-species nuclear transfer at the time of filing. The specification provides a working example of the invention in which human donor oral epithelial cells or human donor lymphocytes are transferred to enucleated bovine oocytes. Following cell fusion and NT unit activation, the resulting activated NT units were cultured for 12 days. On page 32, Table 1, the applicant's report that fusion of human lymphocytes and enucleated bovine oocytes did not result in any NT units with more than 16 cells. Thus, the specification itself provides evidence that not all differentiated donor cells are capable of creating an NT unit capable of giving rise to a multicellular structure of greater than 50 cells. Of the 34 NT units made using human oral cavity epithelium, only 1 NT unit progressed to greater than the 16 cell stage. The specification does not give the exact number of

cells in this NT unit. The working example does not report on the actual structural or functional characteristics of the 1 NT cell mass with greater than 16 cells such that it is unclear whether the cell mass demonstrated cleavage and actually reached a blastocyst stage of development. Further, the single NT unit described was not implanted into a host animal such that potential development of the cell mass into an actual embryo or fetus could be observed. In the absence of any such data, the extent of reprogramming of the donor genomic DNA and thus the totipotency of the NT unit cannot be determined. It is also noted that the working example is limited to the transfer of human differentiated somatic cells to enucleated bovine oocytes. The specification does not provide any working examples using donor cells from any other species than human, or oocytes from any species other than a bovine. Thus, the evidence provided by the working example, which only demonstrates the production of 1 NT unit capable of developing to beyond the 16 cell stage derived from a human epithelial donor cell and a bovine oocyte from 34 human epithelial/bovine oocyte NT units and 18 human lymphocyte/bovine oocyte NT units, is not commensurate in scope with the claims as written. Furthermore, as noted above, it is unclear from the disclosure of the specification whether the single 16+ cell NT unit described is capable of producing an actual blastocyst or capable of giving rise to live animal.

The working example also reports that the growth of a single colony of cells derived from an NT unit which the applicants state had a similar morphology to mouse embryonic stem cells. However, the specification does not provide any actual evidence that the cell colony derived from the NT unit has any actual stem cell properties such as the ability to differentiate into several different cell types, or that the cells are in fact totipotent and capable of developing into a live animal. While the specification teaches that methods were available in the prior art for

inducing the differentiation of embryonic stem cells into various cell types, the working example does not demonstrate or provide any evidence that the cell colony produced from the NT unit is actually a stem cell or is in fact capable of differentiating into any cell type using any of the culture conditions referred to in the specification. In fact, while the working example states that the cells appeared morphologically similar to murine embryonic stem cells, the cells had a slower doubling time than mouse ES cells which suggests that the these cells are not functionally identical to mouse ES cells. Further, since the genomic DNA in this example is human DNA not murine DNA, the significance between any morphological resemblance between the NT derived cell colony and murine embryonic stem cells cannot be determined.

Furthermore, a post-filing review of the exact data presented in the instant specification reveals that the skilled artisan would not accept the working example presented in the specification as evidence for the creation of human embryonic stem cells. Marshall et al. provides a discussion of the data presented in the working example and quotes from various skilled artisans in the field of nuclear transfer regarding the significance of the applicant's data. In the article, Marshall interviewed Dr. Robl, one of the instant inventors, and states, "Robl concedes that the experiment did not yield publishable data. He says he classified the cells as human stem cells based on his experience of 'look[ing] at hundreds and hundreds' of cell colonies. But Robl offered no other data to support this conclusion." (Marshall (1998) Science, Vol. 282, page 1390-1391, see page 1390, second column). Marshall then quotes other researchers who state that Robl and Cibelli didn't do any of the tests normally done to show that these cells were human or that they were stem cells, such as looking for expression of human proteins or growth of specialized tissues. James Thomson, a leading researcher in human stem

cells, is quoted as saying that the cell colony produced by the instant inventors, " meet none of the criteria" for embryonic stem cells, and Gary Anderson is quoted as saying, " Just because someone says they're embryonic stem cells doesn't mean they are" (Marshall, *supra*, page 1390, second column). Thus, the Marshall article demonstrates that the skilled artisan would not accept the data presented in the specification as compelling evidence for the production of actual human stem cells.

Therefore, based on the art-recognized high degree of unpredictability in the art of cross-species nuclear transfer, the evidence provided in the working examples that not all differentiated donor cells can produce a cell mass with at least 50 cells following nuclear transfer into a bovine oocyte, the lack of evidence for actual reprogramming of the differentiated genomic DNA in the 1 NT unit produced that possessed greater than 16 cells, the lack of evidence for the isolation of an actual embryonic or stem cells from the NT unit cell mass, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to make or use the invention as claimed.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 65-67 and 81-84 are newly rejected under 35 U.S.C. 102 (b) as being anticipated by WO 91/08216 (1991), hereafter referred to as Heyneker et al. The applicant claims an isolated embryonic cell or cultured cell derived from an embryonic cell which is not itself an embryo comprising human genomic DNA and bovine mitochondria.

In regards to the "cultured" cells of claims 81-84, please note that "a cultured cell that is derived from an embryonic cell" is essentially a product by process claim. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989).

Heyneker et al. teaches methods of generating transgenic bovine species comprising a transgene encoding a recombinant human polypeptide (Heyneker et al., page 12). The human genomic DNA is "genetically altered" since it has been removed from the total human genome

and placed into a bovine genome. Heyneker et al. further teaches the production of transgenic embryos, in which prior to transplantation, cells are removed from the embryo (Heyneker et al., page 8, lines 11-24). The isolated transgenic cell removed from the bovine embryo is a bovine embryonic cell which comprises human genomic DNA as the transgene and bovine mitochondria. Thus, by teaching all the limitations of the claims as written, Heyneker et al. clearly anticipates the instant invention as claimed.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER